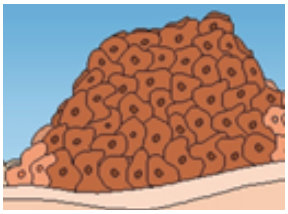

Activity 2

Cancer and the Cell Cycle

At a Glance

Focus: Students use five print-based resources to help them construct an explanation for how cancer develops, then use their new understanding to explain several historical observations about agents that cause cancer.

Major Concepts: The growth and differentiation of cells in the body normally are precisely regulated; this regulation is fundamental to the orderly process of development that we observe across the life spans of multicellular organisms. Cancer develops due to the loss of growth control in cells. Loss of control occurs as a result of mutations in genes that are involved in cell cycle control.

Objectives: After completing this activity, students will

- understand that many different agents can cause cancer,
- understand that cancer represents a breakdown of the processes that regulate the growth of normal cells and tissues,
- recognize that cancer develops as a result of genetic damage that occurs to cells across time,
- be able to explain that cancer is associated with the occurrence of damage to particular classes of genes involved in the normal regulation of the cell cycle, and
- understand that studying the processes involved in the development of cancer has led to a significantly increased understanding of the normal cell cycle as well as to new strategies for treating cancer.

Prerequisite Knowledge: Students should be familiar with mitosis, the cell cycle, and terms such as “gene” and “mutation.”

Basic Science-Public Health Connection: This activity focuses students’ attention on how understanding the basic biology of cancer can help us make sense of the many observations people have made about risk factors related to cancer.

Introduction

Cancer has been described as a single disease and a hundred diseases. The description of cancer as a single disease arises from the observation that all cancers display uncontrolled growth, the ability to expand without limit. The description of cancer as a hundred diseases arises from the observation that cancer can appear as a result of different causes, in a variety of sites within the body, and that each type of cancer displays its own growth rate, prognosis, and treatability.

The discovery that all cancer involves a fundamental disruption in the growth of cells and tissues suggests that to understand cancer, we need to understand the events and processes that occur as both normal and abnormal cells grow and divide. In fact, much cancer research across the past two decades has focused on this challenge. This research has revealed a complex picture of how two classes of

genes, called proto-oncogenes and tumor suppressor genes, normally regulate the intricate sequence of cell cycle events. And it also has revealed how the accumulation of mutations in these genes can contribute to the development of an altered cell, a cell that has lost the normal controls on cell division.

In this activity, students gain a flavor of the initial confusion that existed among scientists about the causes of cancer by viewing several early accounts of possible relationships between the development of cancer and various internal and external factors. Students then use five print-based resources to learn about evidence that helped scientists understand that (1) cancer involves the uncontrolled division of body cells; (2) cell division normally is precisely regulated; (3) cell cycle regulation is accomplished by two major types of genes; (4) cancer-causing agents often damage genes; and (5) when damage occurs to genes that regulate the cell cycle, the balance between signals that stimulate cell division and signals that inhibit cell division can change, leading the cell to divide more often than it normally would. As the activity closes, students use their new understanding of cancer to explain the relationships they learned about in Step 1.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 2.1, *News Alerts* (make 1 copy per student)
- Master 2.2, *Understanding Cancer* (make 1 copy per student)
- Master 2.3, *Resources for Understanding Cancer (*make 1 copy per student)

Procedure

1. **Introduce the activity by noting that people have wondered about the cause of cancer for thousands of years. Throughout this time, many correlations have been noted between the development of cancer and various internal and external factors. As examples of this, distribute one copy of Master 2.1, *News Alerts,* to each student and ask students to organize into their teams and read each of the items. Then distribute one copy of Master 2.2, *Understanding Cancer,* to each student and ask students to complete Section 1, Factors Reported to Be Associated with Cancer, by identifying**

   - **what each item suggests about the cause of cancer and**
   - **what evidence the item provides to support the claim.**

   Divide the class into teams for this activity. We recommend that you ask students to organize into the same teams in which they worked in Activity 1. This arrangement has the advantage that students who worked together in Activity 1 will work together in this activity as well.

   Give the teams approximately 5 minutes to complete this task.

   Notice that the *News Alert* items describe reports of relationships between cancer and various causative agents that span more than 200 years. You may wish to draw students' attention to the length of time people have systematically studied the cause of cancer and also to the

diversity of relationships that scientists studying the disease have identified and explained.

2. **Ask the students what each item suggests about the cause of cancer and what evidence was provided to support the claim.**

   To increase the level of student participation, ask one team to describe what a particular item suggests about the cause of cancer and a different team to describe the evidence on which this claim was based.

   At the close of the reporting, you may wish to ask students whether the evidence presented in these *News Alert* items is convincing and why. This is a good point in the activity to remind students of the difference between correlation and causation and ask what type of evidence would demonstrate causation.

3. **Explain that each item describes what has proven to be a real relationship between the development of cancer and the factor described. Ask students what general question all four items raise when they are considered collectively.**

   Students may suggest several questions that could be asked. Help students see that the fundamental challenge facing scientists interested in understanding cancer was to explain how so many diverse factors can cause it. Students may phrase this question as "How can so many different factors all cause cancer?" or "What does each of these factors do to cause cancer?"

   Tip from the field test. Students may ask questions that relate more to the medical aspects of cancer than to its underlying cause. If students are having difficulty recognizing the question that these four videos raise about cancer's cause, you may wish to rephrase the question as "What do you think may have confused researchers trying to understand what goes wrong in cancer cells?" or "The number of different agents that can cause cancer was one of the most confusing aspects of cancer to early researchers. Why was this confusing?" or "What do you think all these agents had in common and why was it important to discover that?"

4. **Explain that research across the past 30 years has helped scientists understand how so many different factors can cause cancer. Distribute one copy of Master 2.3, *Resources for Understanding Cancer,* to each student and explain that next students will read five resources that will help them construct an explanation of the cause of cancer. They then will use their understanding of cancer's cause to explain the relationships described in the *News Alert* items.**

5. **Direct the students to read *Resources for Understanding Cancer*. Then ask them to complete Section 2, Building an Explanation for the Cause of Cancer (on *Understanding Cancer*) by writing a one-sentence statement that summarizes what they learned from each resource.**

Students may be surprised to learn about the cell cycle in an activity that focuses on risk factors for cancer. Point out that understanding disease typically requires scientists to examine basic cellular processes, and that understanding those processes can, in turn, help health care workers develop better prevention and treatment strategies.

- *Resource 1* (the explanation of abnormal cell growth) should lead students to conclude that **cancer involves the uncontrolled division of body cells**.
- *Resource 2* (the introduction to the cell cycle) should lead students to conclude that **cell division normally is precisely regulated**.
- *Resource 3* (the information on proto-oncogenes and tumor suppressor genes) should lead students to conclude that **cell cycle regulation is accomplished by two major types of genes**.
- *Resource 4* (the information on the mutagenicity of carcinogens) should lead students to conclude that **cancer-causing agents often damage genes**.
- *Resource 5* (the information on the effect of damaging cell cycle genes) should lead students to conclude that **when damage occurs to genes that regulate the cell cycle, the balance between signals that stimulate cell division and signals that inhibit cell division can change, leading the cell to divide more often than it normally would**.

Steps 6–8 represent the closure steps for this activity. Step 6, in particular, focuses students' attention on the activity's major concepts.

6. **After the students have completed Section 2 on *Understanding Cancer*, point out that their five statements constitute a basic explanation of what goes wrong when a cell becomes cancerous. Ask one or more teams to read their statements to the class, then invite clarifying comments and questions from the rest of the students.**

7. **Ask the teams to complete Section 3, Explaining Factors Associated with Cancer, on *Understanding Cancer* by reviewing the information in Section 1 and writing four one-sentence explanations for how the relationship each *News Alert* item describes can be understood in the light of what scientists know today about the cause of cancer.**

   Give students approximately 5 minutes for this task, then ask a spokesperson from each team to explain one of the items.

   Students may have difficulty with this step, primarily because they lack sufficient background in biology to make the connections required to explain "causative" agents of cancer. For this reason, we suggest that you ask your students to provide only the most basic explanations, such as those provided in bold type below. After they have done so, you can explain as much of the detail as you think is appropriate and will be interesting to the class.

   - *News Alert! Cancer and Chemical Poisons.* Students should be able to suggest that **a chemical in the coal dust caused damage to genes that regulate the cell cycle.**

     Pott was probably the first person to associate a specific type of cancer (scrotal cancer) with a specific occupation (chimney sweeping). Pott believed the problem was the coal soot that caught in the skin folds of the scrotum. In 1918, coal tar was shown to cause skin cancer in rabbits, and in 1924 the causative agent was identified as polycyclic aromatic hydrocarbons, especially benzo (a) pyrene.

- *News Alert! Cancer and Your Family History*. Students should be able to suggest that **children with inherited retinoblastoma have inherited an error (mutation) in a gene that regulates the cell cycle.**

  Retinoblastoma, a relatively rare cancer, is a highly malignant tumor of the eye. If left untreated, the malignancy moves from the eye along the optic nerve to the brain, from where it metastasizes to other tissues. Slightly more than one-third of retinoblastoma cases are inherited. The remaining cases are sporadic (not inherited). The age of onset of the inherited type is approximately 10 months, on average 8 months earlier than the sporadic type. Tumors of both eyes occur only with the inherited type.

  A mutation or deletion in the long arm of chromosome 13 is associated with the development of retinoblastoma. Both alleles of the gene involved, the *RB* gene, are either missing or altered in nearly every case of retinoblastoma (whether inherited or sporadic). The gene's normal product has an inhibitory effect on cell division.

  Children who inherit an altered allele of the *RB* gene are heterozygous for the chromosome 13 abnormality. They are at high risk for developing retinoblastoma because only a single mutation or deletion of the normal *RB* gene will result in a cell initiating uncontrolled cell division. The mutation rate for this gene is high enough that there is significant risk of experiencing the mutation in the cells of both eyes (thus, the risk of developing retinoblastoma in both eyes in the inherited type).

  In sporadic (nonhereditary) retinoblastoma, both alleles of the *RB* gene are normal, and each one must be mutated in the same cell for the tumor to arise. In contrast with hereditary retinoblastoma, the likelihood of this occurring in both eyes is so low that for all practical purposes, it does not occur.

- *News Alert! Cancer and Radiation Exposure.* Students should be able to suggest that **exposure to X-rays damages genes that regulate the cell cycle.**

  Ionizing radiation is a well-known human carcinogen. The first reports of association between X-rays and cancer appear in the literature in the early 1900s. Subsequent reports include the association between radium exposure and leukemia (for example, Marie Curie died of leukemia); radium exposure and osteosarcomas (for example, cancer developed among painters of luminescent dials in watch factories in the 1930s); and radiation from nuclear tests and cancer (for example, children in the Marshall Islands exposed to radioactive iodine released from a nuclear test displayed a significant increase in thyroid cancer).

  Carcinogenesis from ionizing radiation is believed to occur through the formation of mutagenic oxygen free radicals. Ionizing radiation is clearly carcinogenic when presented at unusually high doses, but it has been difficult to quantify its effect when presented at low doses. Because the assumption is that any amount of exposure has some effect, federal regu-

lations mandate that exposure to radiation be kept "as low as reasonably achievable."

- *News Alert! Cancer and UV Light.* Students should be able to suggest that **exposure to UV light damages genes that regulate the cell cycle.**

  The relationship between sun exposure and skin cancer has been clarified greatly across the past century. In the late 1800s, observers noticed that sailors exposed to the sun developed a variety of abnormal lesions called "sailor's skin," and in the early 1900s, an increased risk of skin cancer was observed among farmers. By 1928, researchers had demonstrated the carcinogenic effect of UV radiation on the skin of laboratory animals. Today, scientists recognize excessive exposure to UV radiation (whether from the sun or other sources) as a key risk factor for skin cancer.

Steps 6 and 7 provide excellent opportunities to assess students' understanding of the activity's major concepts. In Step 6, students should be able to express five key ideas about the regulation of cell division, and in Step 7, they should be able to apply this understanding to explain how certain risk factors increase a person's chance of developing cancer.

8. **Close the activity by asking students what the activity reveals about science's ability to bring order to even the most bewildering set of observations.**

   Students should recognize that science helps us explain and relate observations that we make about the natural world. You may wish to ask students if they can think of other examples of observations that have been organized and made comprehensible through the work of science. Students may propose the atomic theory, the cell theory, and the germ theory of disease as important organizing explanations in science. If they do not mention evolution, point out that evolution is the most important organizing explanation in biology.

News Alerts

News Alert!
Cancer and Chemical Poisons
Dr. Percivall Pott
London, 1775

I have been studying the various forms of cancer that plague our society. It has come to my attention that people of certain occupations have higher frequencies of certain types of cancer than the general public. In particular, chimney sweeps have a high rate of cancer of the scrotum. Young boys often enter the profession because they are able to squeeze down narrow chimneys. Once inside the chimneys, they spend hours scraping them clean of the accumulated tars that otherwise would cause disastrous chimney fires. Sweeps are continually covered with flue tar and dust, and because they likely do not bathe regularly, this dust remains trapped in the folds of the skin. I believe that some agent in the coal tar, when exposed to the scrotum across many years, actually causes this disease.

News Alert!
Cancer and Your Family History
Dr. Hilario de Gouvea
Brazil, 1886

Today I would like to present a most curious case. It may shed light on an aspect of cancer about which we know little. Fourteen years ago, a man brought his 2-year-old son in for treatment of retinoblastoma, a very rare form of cancer that develops within the eye, often of young children. If untreated, the cancer travels up the optic nerve until it reaches the brain and spreads throughout the body. I removed the tumor, and the boy was completely cured. He married and had seven children. Curiously, two of his girls developed retinoblastoma in both eyes. The parents refused treatment, and both girls died within several months. Here, a form of cancer that normally occurs once in every 20,000 children has occurred three times in one family. I believe this represents evidence that susceptibility to cancer can be transmitted from parents to children, just like hair or eye color.

News Alert!
Cancer and Radiation Exposure
X-Ray Technician
New York, 1902

X-rays are the marvel of modern science. These powerful yet invisible rays permit us to see the inner workings of the body and provide treatments that we are just beginning to understand. Let technicians be warned, however, these rays, while capable doing great good, can also do great harm. We have noticed a high rate of skin cancer among technicians who use their hands to focus the energized machine. Patients are exposed only briefly to the these rays. Technicians, on the other hand, work on these machines all day long and have many hours of exposure. Our advice is to keep the machine off while adjusting it and even to go to the next room when it is time to energize it.

News Alert!
Cancer and UV Light
News Reporter
Miami, 1945

Now that the war is over, Americans are ready to relax and enjoy their freedom. What better place to recuperate than at the beach? Women have cast aside the Victorian fashions of yesteryear and have adopted the new, sleek, trimmed-down swimsuit. Sunbathers say the more skin, the better. Be warned, however, that all this skin and sun can lead to painful burns. In fact, now doctors are warning of a possible connection between the sun's rays and skin cancer. Perhaps the unseen ultraviolet rays that fade our clothes can also damage skin and lead to deadly disease. Maybe a healthy tan is not so healthy after all.

Understanding Cancer

Use the resources provided to complete this worksheet.

Section 1: Factors Reported to Be Associated with Cancer
Read the *News Alert* items and use the information provided to identify what each item suggests is the cause of cancer and what evidence supports that claim.

News Alert	Factor Proposed to Cause Cancer	Evidence
Cancer and Chemical Poisons		
Cancer and Your Family History		
Cancer and Radiation Exposure		
Cancer and UV Light		

Section 2: Building an Explanation for the Cause of Cancer
Read the resources on *Resources for Understanding Cancer*. Think about the information each resource presents, then write a one-sentence statement for each that summarizes what you learned.

Resource 1:
Cancer involves . . .

Resource 2:

Cell division normally is . . .

Resource 3:

Cell cycle regulation is accomplished by . . .

Resource 4:

Cancer-causing agents often . . .

Resource 5:

When damage occurs to genes that regulate the cell cycle . . .

Section 3: Explaining Factors Associated with Cancer

Review your notes from Section 1, then write a sentence that describes how our current understanding of cancer explains the role that each factor plays in causing cancer.

Cancer and Chemical Poisons

Cancer and Your Family History

Cancer and Radiation Exposure

Cancer and UV Light

Resources for Understanding Cancer

Resource One

The rate and timing of cell division in your body normally are very precisely regulated. Cells are formed, mature, and eventually die.

As this happens, new cells divide, creating replacement cells. Chemical messengers that pass between neighboring cells help keep the rate of cell division equal to the rate of cell death.

Sometimes, a cell breaks free from its normal restraints and begins to follow its own pattern of cell division. This precancerous cell divides more often than normal, eventually producing a mass of cells that also divide more often.

Further changes in these cells can increase the frequency of cell division even more, until eventually a cancerous tumor develops.

At this point, the tumor grows large, but is confined to the tissue where it originated. Late in the development of cancer, some cells may gain the ability to move into blood vessels and travel to other parts of the body.

Resource Two

For many years, it was a mystery to scientists how cells controlled their cell division. Scientists now know that the chemical messages that cells receive from neighboring cells affect a complicated group of molecules in the cell. These molecules are called the "cell cycle clock."

The cell cycle clock integrates the mixture of signals the cell receives from its neighbors and determines whether the cell should move through each stage of growth and division. If the answer is "yes," the cell grows and divides.

The cell cycle is composed of four phases. In the G_1, or Gap 1, phase, the cell increases in size and prepares to copy its DNA.

Once all the necessary molecules are made, the clock moves the cell to the S phase, called S for "synthesis." This is when the cell copies its DNA.

After the DNA is copied, a second gap period, called G_2, occurs, and then the cell divides. The phase in which the cell divides is called M, for mitosis.

The new daughter cells immediately enter G_1. Depending on the signals they receive from neighboring cells and the decisions their cell cycle clocks make, they may go through the cell cycle again or stop cycling temporarily or permanently. Thus, in normal tissues, cell growth and division is precisely controlled by internal clocks.

Resource Three

Two types of genes play a major role in regulating the cell cycle. Genes called proto-oncogenes encourage cell division. Proteins produced by these genes act like accelerators, stimulating the cell to grow and divide.

In contrast, genes called tumor suppressor genes inhibit cell division. Proteins produced by these genes act like brakes to slow down or stop cell division.

The balance between the activities of proto-oncogenes and tumor suppressor genes keeps normal cells dividing at a rate that is appropriate for their position and role in the body.

Resource Four

An important milestone in scientists' efforts to understand cancer came in the 1970s when it was shown that many cancer-causing agents also are able to cause changes in DNA that we call mutations.

In fact, research showed that in many cases, chemicals that are powerful cancer-causing agents also are powerful mutagens. Mutagens are agents that produce mutations. This is shown here on a graph that compares the ability of several chemicals to cause cancer with their ability to cause mutations.

In contrast, chemicals that had only a weak ability to stimulate the development of cancer were only weak mutagens.

We now know that some cancer-causing agents do not fit this simple pattern. But the fact that many cancer-causing agents also cause mutations gave scientists an important clue about what might cause cells to become cancerous.

Resource Five

Normal cell division in the body depends on a precisely regulated set of events that determine when a cell will divide and when it will not divide. Two types of genes, called proto-oncogenes and tumor suppressor genes, are primarily responsible for this regulation.

When mutated, however, proto-oncogenes can become what scientists call "oncogenes," genes that stimulate excessive division. This situation is similar to getting a car's accelerator stuck in the downward position: A cell that experiences such mutations tends to divide more frequently than it normally would.

In contrast, mutated tumor suppressor genes can become inactive. A cell that experiences a mutation in a tumor suppressor gene loses some of its crucial braking power. Again, the result is a tendency for the cell to divide more frequently than it normally would.

For a cancerous tumor to develop, mutations must occur in several of a cell's division-controlling genes. These mutations disturb the balance that normally exists between signals that stimulate cell division and signals that inhibit cell division. The result is uncontrolled division.